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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,524	08/15/2001	Andrew N. Shelling	3911-10	9590

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NIXON & VANDERHYE, PC
1100 N GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

EXAMINER
JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,524	SHELLING, ANDREW N.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0203* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This application is a 371 of PCT/NZ00/00021, filed February 25, 2000. The International Search Report and International Preliminary Examination Report for PCT/NZ00/00021 have been received and considered.

2. The Amendment filed December 28, 2001, the paper and computer readable forms of the Sequence Listing filed December 28, 2001, and the Response filed January 31, 2003 have been entered.

Election/Restriction

3. Applicant's election of Group I in the Response filed January 31, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. In the Response of January 31, 2003, Applicant canceled all of the non-elected claims (claims 11-14), as well as claim 9. Accordingly, claims 1-8 and 10 are now pending and under consideration.

Information Disclosure Statement

5. It is noted that on January 31, 2003, applicant filed an IDS including a PTO-1449; however, no reference copies were provided with this submission, and applicant indicated that the references would be provided in a supplemental paper. On February 6, 2003, an IDS including references and a duplicate of the PTO-1449 filed January 31, 2003 were filed. Accordingly, the examiner has considered the submitted references,

and has provided herewith a signed and initialed copy of the PTO-1449 filed February 6, 2003.

Regarding the Pampfer et al reference, it is noted that the IDS fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of this publication that is not in the English language. As the reference includes an English language abstract, the examiner has added the notation "abstract only" to the 1449 and initialed so as to indicate that the English abstract has been considered.

Oath/Declaration

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it does not refer to PCT/NZ00/00021, of which the instant application is a 371. While the instant application has been accepted for examination (see the Form 903 mailed September 26, 2001), a new oath/declaration is required, which oath/declaration should indicate that the instant application "was filed as PCT international application no. PCT/NZ00/00021 on February 25, 2000."

Sequence Identifiers

7. The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a) and (a)(2). However, the specification fails to comply with one or more of the requirements of 37 CFR § 1.821 through 1.825 because the specification recites sequences that lack description by the appropriate sequence identifier set forth in the "Sequence Listing" as required by 37 CFR § 1.821(d). See Figures 2-3 and the Descriptions thereof, neither of which include the SEQ ID Nos that correspond to the sequences depicted in the Figures. Appropriate corrections for compliance are required. Specifically, Applicant must either file substitute Figures that recite the appropriate sequence identifiers, or amend the brief description of the figures so as to set forth said sequence identifiers. See *MPEP* 2422.02.

Specification

8. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

9. The title of the invention is not descriptive of the elected invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Diagnosis of premature ovarian failure.

10. The use of the trademark LYMPHOPREP™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-8 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of determining whether a human female subject is predisposed to premature ovarian failure (POF) by detecting the presence of a G769A transition in the INHα gene, does not reasonably provide enablement for methods of determining whether any "female subject" is predisposed to POF by detecting the presence or absence of any type of "alteration" in any "gene encoding inhibin". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the

existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

The instant claims are drawn to a method "of testing to detect whether a female subject is predisposed to Premature Ovarian Failure (POF) which comprises the step of detecting the presence or absence of an alteration in the gene encoding inhibin, wherein the presence of an alteration is indicative of a predisposition to POF." Dependent claims 2-6 further require analysis of nucleic acids to accomplish detection of the alteration, with claim 4 particularly requiring RFLP analysis using restriction enzyme Bst71I. Dependent claims 7-8 further require analysis of amino acid sequences to accomplish detection of the alteration. Finally, dependent claim 10 requires a method "in which the presence of a G → T substitution at nucleotide 769 of INHα is indicative of a predisposition to POF."

The specification discloses the existence of two different forms of inhibin: inhibin A, which is a heterodimer of α and βA subunits, and inhibin B, which is a heterodimer of α and βB subunits (see page 5). The specification further teaches that "The inhibin subunits are encoded by three separate genes: INHα, INHβA, and INHβB" (see page 5). The specification exemplifies a particular polymorphism in the INHα gene, the G769A polymorphism, which encodes an Ala257Thr substitution in the encoded inhibin subunit; this particular polymorphism was found to occur in subjects from two different populations of human POF patients, and to be absent from normal populations (see, e.g., pages 15-16). Accordingly, given the guidance provided by the specification,

detection of the presence of the G769A polymorphism of the INHα gene is one factor that one of skill in the art would reasonably consider in determining whether a human female subject was predisposed to POF. The specification also teaches a second inhibin gene polymorphism, a C1032T polymorphism in the INHβA gene (see, e.g., pages 15-16). However, the specification discloses that this polymorphism is a silent substitution that does not alter the amino acid sequence of the encoded inhibin subunit (see, e.g., page 16, lines 1-4), and the specification does not provide any evidence that this particular polymorphism is associated with POF. Further, the specification does not provide evidence of the existence of any other inhibin gene polymorphisms or alterations that are associated with POF.

It is unpredictable as to whether one of skill in the art could use the instant invention in a manner reasonably commensurate with the claims. The instant claims are extremely broad, encompassing detection of virtually any polymorphism in any inhibin gene as an indicator of POF in any type of female subject. However, as discussed above, the specification discloses only a single particular polymorphism in a single human inhibin gene that has been shown to be indicative of a predisposition to POF in human female subjects. Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance and enablement of a claimed invention. However, in the instant case, the closest prior art reference, Petraglia et al (Fertility and Sterility 70(5):907-912 [11/1998]) teaches only that serum concentrations of inhibin A and inhibin B are significantly lower in women with POF than in control subjects (see entire reference, particular Figures 1-2). While Petraglia et al

teach that the lower circulating inhibin levels in POF patients "reflect ovarian failure" (see page 911), Petraglia et al do not provide evidence of the existence of any polymorphisms or alterations in either the genes encoding inhibin A or the genes encoding inhibin B that might be responsible for POF or predisposition thereto. Further, it is well known to those of skill in the art that while such a decrease in protein concentrations might arise from, e.g., a promoter mutation that results in decreased expression of an inhibin gene, a multitude of other factors (e.g., alteration in the structure or expression of a transcription factor that affects inhibin expression) could also be the cause of such a decrease. Further, Petraglia et al provide no evidence of structural differences in the inhibin proteins of the type exemplified in applicant's specification, and the prior art is silent with respect to any inhibin gene polymorphisms that are associated with POF. Given the high skill level of one of skill in the relevant art, it would clearly be within the ability of such an artisan to conduct further experimentation to determine the cause of the decreased circulating inhibin demonstrated by Petraglia et al. Further, one of skill in the art could clearly perform further experiments to detect the existence of other inhibin gene polymorphisms, and to establish whether such polymorphisms are associated with POF. However, as the outcome of such further experiments cannot be known in advance, it is unpredictable as to what such experiments might reveal, and as to whether any quantity of experimentation would be sufficient to identify any inhibin gene polymorphisms other than the particular INHα gene polymorphism exemplified by applicant that are actually associated with POF. Furthermore, it is noted that the instant claims encompass methods performed on any

type of "female subject." While it is well known to those of skill in the art that inhibin genes are found in animal species other than humans (see, e.g., Stewart et al, FEBS Letters 206(2):329-334 [10/1986]), neither the specification nor the prior art provide any evidence of the existence of any inhibin gene polymorphisms in non-humans that are associated with POF. It is unpredictable as to whether any such polymorphisms exist, and it is unknown as to whether any amount of experimentation would result in the identification of a polymorphism or polymorphisms in any inhibin gene of a non-human subject that is associated with POF. Accordingly, while one of skill in the art could clearly practice methods of determining whether a human female subject is predisposed to POF by detecting the presence of a G769A transition in the INHα gene, it would require undue experimentation to use the invention in a manner reasonably commensurate with the claims.

With further regard to claim 4, it is noted that the claim is limited to restriction digestions that employ Bst71I. However, while the specification discloses that digestion of INHα with Bst71I allows detection of the G769A polymorphism, the instant claims are not limited to INHα. As neither the prior art nor the specification provide any evidence that digestion with Bst71I allows detection of a polymorphism related to POF in an inhibin gene other than INHα, and further, as claim 4 is not limited to human subjects, it would require undue experimentation to practice the method of claim 4.

With further regard to claim 10, it is noted that while the specification exemplifies a G769A polymorphism of INHα that is associated with POF, claim 10 as written refers to a G769T polymorphism. Neither the specification nor the prior art provide evidence

that such a polymorphism is associated with POF. Further, claim 10 as written encompasses non-human subjects. Accordingly, it would require undue experimentation to practice the method of claim 10 as now written.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-8 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 and 10 are indefinite over the recitation of the limitation "detecting the presence or absence of an alteration in the gene encoding inhibin" in claim 1. The specification at page 3 provides a definition for the term "gene encoding inhibin," stating that "the term 'gene encoding inhibin' means INHα, INHβA, and INHβB, together with their non-coding flanking sequences and regulatory elements." Further, applicant states on page 5 that "INHα, INHβA, and INHβB, together with their non-coding flanking sequences and regulatory elements are collectively referred to herein as the 'gene encoding inhibin.'" However, the specification and the prior art as exemplified by Stewart et al (FEBS Letters 206(2):329-34 [10/1986]) also teach that the three molecules disclosed by applicant as constituting the "gene encoding inhibin" are not in fact part of a single gene, but rather three different genes (in the specification, see page 5, lines 25-26, which states that "The inhibin subunits are encoded by three separate genes: INHα, INHβA, and INHβB; in Stewart, see entire reference, particular page 333, left column). Further, while a literal reading of applicant's definition of "gene encoding

inhibin" suggests that one must detect an alteration in "INHα, INHβA, and INHβB" (i.e., in three different molecules) in order to meet the requirements of the claims, applicant's claim 10, which requires detection of an alteration in a single one of these genes, suggests that detection of an alteration in one of INHα, INHβA, and INHβB is sufficient to meet the claims. Accordingly, taking into consideration the teachings of the specification, the language of the claims, and the teachings of the art, it is unclear as to whether the recitation "the gene encoding inhibin" is intended to refer to one of INHα, INHβA, and INHβB or to all of these molecules, and thus it is further unclear as to what type of alteration or alterations must actually be detected in order to meet the limitations of the claims. It is also noted that claim 1 does not previously refer to, e.g., "a gene encoding inhibin;" accordingly, antecedent basis for the limitation "the gene encoding inhibin" has not been provided.

Claims 3 and 6-8 are indefinite over the recitation of the limitations "the DNA sequence coding for wild-type inhibin" in claim 3, "the mRNA sequence transcribed from DNA coding for wild-type inhibin" in claim 6, "the expressed inhibin protein" and "the amino acid sequence of the expressed inhibin protein" in claim 7, and "the expressed inhibin protein" and "the amino acid sequence of wild-type inhibin protein" in claim 8, respectively. While the recitation of, e.g., "DNA coding for inhibin" in claim 2 is merely a broad recitation that could encompass any "DNA coding for inhibin" (e.g., DNA coding for any of INHα, INHβA, and INHβB), the claim language in claims 3 and 6-8 noted above appears to be intended to refer to a particular sequence or molecule (to, e.g., "the" DNA coding for inhibin or "the" expressed inhibin protein). Definitions for these

particular recitations in the claims are not provided in the specification, and as discussed above, there are multiple inhibin genes known in the art. Thus, it is unclear as to whether the recitation of, e.g., 'the DNA sequence" or "the mRNA sequence" coding for inhibin is intended to refer to a particular sequence or sequences (and if so, which one), to any inhibin sequence, etc., and as to whether the recitation of, e.g., "the expressed inhibin protein" is intended to refer to a particular protein or proteins (and if so, which one), to any inhibin protein, etc. It is also noted that the claims do not provide antecedent basis for any of the recitations in claims 3, 6, 7, and 8 set forth above. Accordingly, the claims are vague and indefinite, and clarification is required.

Conclusion

15. The art made of record and not relied upon is considered pertinent to applicant's disclosure. In references published subsequent to the filing of the instant application, Shelling et al (Human Reproduction 15(12):2644-2649 [12/2000]) and Marozzi et al (Human Reproduction 17(7):1741-1745 [7/2002]) provide evidence of an association between the G769A polymorphism and POF in human females (in Shelling et al, see entire reference, particularly pages 2647-2648; in Marozzi et al, see entire reference, particular page 1743). Marozzi et al further teach a polymorphism located upstream of the human INHalpha gene that occurs at a high prevalence in POF patients (see entire reference, particularly page 1744).

16. It is noted that claim 10 of PCT/NZ00/00021 is identical to instant claim 10.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is

703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
April 7, 2003